REMARKS

Applicants first kindly thank Examiner Rao for the teleconference of October 24, 2011, during which Applicants' representative discussed with the Examiner her preferences for excluding subjects with cancer pain and presenting evidence to show that flupirtine would not have been considered an NMDA receptor antagonist.

In response to the Office Action mailed September 13, 2011, Applicants have canceled claims 43-49 and 51 and added new claims 52-59. No new matter has been added. The above amendment is not to be construed as acquiescence with regard to the Examiner's rejections and is made solely to clarify particular aspects of the presently claimed invention, without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendment, claims 52-59 are pending and under examination.

The specification has also been amended to correct certain typographical errors. No new matter has been added by the amendments to the specification, support for which can be found in the specification, for example, at page 26, lines 10-12, and elsewhere.

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

OBJECTIONS TO THE SPECIFICATION

The specification is objected to because the context of the term "disease condition" at page 26, lines 3 and 7-8 appears to be inappropriate.

Applicants thank the Examiner for pointing out these inadvertent typographical errors, and note that they have been corrected in a way that is believed to be consistent with the present invention. The specification at page 26, lines 3 and 7-8 now recites, respectively, "an effective amount of an **analgesic agent such as an opioid** and an amount of flupirtine…" and "[a]dministration of the **analgesic agent** may be sequential or simultaneous or independent of the flupirtine." These amendments are supported by the description at page 26, lines 10-12, and elsewhere, and are believed to add no new matter.

Applicants submit that the objection to the specification has been overcome, and respectfully requests its withdrawal.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 43-49 and 54 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. It is alleged that the term "non-cancer related neuropathic pain" is new matter.

Applicants respectfully traverse this rejection. Nonetheless, without acquiescence or prejudice, the term "non-cancer related neuropathic pain" has been removed from the claims, rendering this rejection moot.

Applicants submit that the instant claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS

Claims 43-49 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, for alleged lack of written description. It is alleged that the term "non-cancer related neuropathic pain" is unclear.

Applicants respectfully traverse this rejection. Nonetheless, without acquiescence or prejudice, the term "non-cancer related neuropathic pain" has been removed from the claims, rendering this rejection moot.

Applicants submit that the instant claims satisfy the definiteness requirement under 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45, 48-49, and 51 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (U.S. Patent No. 5,521,178) in view of Williams *et al.* (U.S. Application No. 2004/0076648), Chizh *et al.* (U.S. Application No. 2004/0092531), and Schwartz *et al.* (U.S. Patent No. 5,721,258). The Action alleges that Nickel *et al.* teach the combination of an opioid and flupirtine for treating pain, but agrees that Nickel *et al.* do not teach that same combination for treating neuropathic pain. The Action, however, alleges that

Williams *et al.* and Chizh *et al.* teach the combination of an opioid and the NMDA receptor antagonist ketamine for treating neuropathic pain, and further alleges that Williams *et al.* and Schwarz *et al.* suggest that flupirtine was considered an NMDA receptor antagonist equivalent to ketamine. The Action then alleges that it would have been obvious to replace ketamine with flupirtine, for use in combination with an opioid to treat neuropathic pain.

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (U.S. Patent No. 5,521,178) in view of Williams *et al.* (U.S. Application No. 2004/0076648), Chizh *et al.* (U.S. Application No. 2004/0092531), Schwartz *et al.* (U.S. Patent No. 5,721,258), and Perovic *et al.* (*Neurodegeneration.* 4:369-374, 1995). The Examiner agrees that the references in A above do not teach the lack of overt sedation, but alleges that Perovic *et al.* remedy this deficiency.

Applicants respectfully traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness. Mainly, Applicants submit that the **unexpected synergism** shown for the claimed combination of flupirtine and an opioid represent secondary considerations of non-obviousness that are sufficient to overcome any alleged *prima facie* case of obviousness.

Merely to re-emphasize, Applicants have shown at least **two** clinically-exceptional results for the combination of flupirtine and an opioid:

(**1**) it creates positive **synergy** in treating neuropathic pain, and

(**2**) it does so without magnifying the **shared** side-effects of these two drugs.

Specifically, Applicants have previously submitted a Declaration showing that the claimed combination of drugs can achieve the same analgesia as each individual drug alone by using only 10% of the ED_{50} dose of each drug – allowing a **90% reduction** in the dosage of each individual drug. In the world of neuropathic pain management, this result is clinically staggering. As further evidence, the treatments in Goodchild *et al.* (*Pain Medicine*. 9:939-949, 2008) significantly improved overall cancer pain scores (*see* Table 3; ranging from about 20-54% improvement), but even more so, they substantially and therefore selectively improved neuropathic cancer pain scores – *see* Table 4; showing **40-798%** improvement with most values being **far greater than 100%**. All of this was achieved without increasing the shared side effects of these drugs, such as sedation, dizziness, nausea, and vomiting, an entirely unexpected finding

in its own right. As discussed below, neither of these results, let alone the combination of both results, could have been reasonably predicted at the time of filing.

Based on the Action's discussion, the main thrust of Applicant's argument is that a person of ordinary skill in the art at the time of filing would not have considered flupirtine to be an NMDA receptor antagonist. That is, there would have been no expectation of functional equivalence between flupirtine and the NMDA receptor antagonist ketamine. Even though ketamine had been shown to further reduce neuropathic pain when combined with an opioid, relative to either agent alone, there would have been no reason to expect flupirtine to have that same effect, let alone a **synergistic effect** when combined with an opioid. A person of ordinary skill in the art would have thus had no technical reason to expect the synergism shown by Applicants for the combination of flupirtine and an opioid in treating neuropathic pain.

For at least two reasons, discussed in greater detail below, a person of ordinary skill in the art at the time of filing would **not** have considered flupirtine to be an NMDA receptor antagonist. First, it was well-understood in the art that receptor antagonists **must** physically bind to their target receptors, and it had been empirically shown by at least two careful, pre-filing date studies (after Schwarz *et al.*) that flupirtine does not bind to the NMDA receptor; instead, it had been empirically shown to be an opener of a family of potassium channels variously known as Kv7 channels, G-coupled inwardly rectifying potassium channels (GIRK) and KCNQ-channels. Flupirtine was thus not considered an NMDA receptor antagonist within the art-accepted meaning of that term at the time of filing, nor has it been since that time.

Also, even assuming allegations of a **so-called** "functional" NMDA receptor antagonism (*see* the Action, page 12, discussing Schwarz *et al.* and Kornhuber *et al.*), the levels of flupirtine required to antagonize inward current responses to NMDA were shown to be so high as to be clinically-irrelevant, *i.e.*, likely toxic and thus clinically useless. For methods of treating a mammal, as claimed, a person of ordinary skill in the art of treating neuropathic pain would not have considered this alleged "functional" NMDA antagonism at all relevant to flupirtine's potential as a clinical agent.

Flupirtine was not considered an NMDA "receptor antagonist" within the art-accepted meaning of that term. At the time of filing, the term "antagonist" referred to molecules that **bind** to certain proteins at a specific site on that protein in order to suppress or inhibit the activity of

that protein. *See* Item 11 of the § 1.132 Declaration of Professor David Adams, Ph.D (the Adams Declaration, attached). Accordingly, the term "NMDA receptor antagonist" would have been understood to refer to a molecule that binds to an NMDA receptor at a specific site on the NMDA receptor in order to suppress or inhibit the activity of the NMDA receptor. *Id*. However, the binding studies of Osborne *et al.* (*Invest. Opthalmol. Vis. Sci.* 37: 274-280, 1996) failed to indentify any detectable affinity of flupirtine to the known binding sites of the NMDA receptor, and Jakob and Krieglstein (*British Journal of Pharmacology*. 122:1333-1338, 1997) concluded that 1000 μM flupirtine did not directly affect NMDA-induced currents in rat cultured hippocampal neurons by use of the whole-cell configuration of the patch-clamp technique – the **gold-standard** in characterizing ion channel physiology. *See Id*. at 1333, 1336. Prior to the time of filing, two careful and independent studies had empirically shown that flupirtine does not bind to the NMDA receptor, even at high concentrations. Based on these studies, and despite the earlier and less-focused studies of Schwarz *et al.* and the mere boilerplate of Williams *et al.*, a person of ordinary skill in the art would **not** have considered flupirtine to be an NMDA receptor antagonist, and thus would **not** have associated flupirtine and ketamine as functional equivalents for this purpose.

Further, even the alleged "functional" NMDA receptor antagonism of flupirtine would not have created the expectation that ketamine and flupirtine are functional equivalents, at least for clinically-relevant concentrations of flupirtine. Here, the Action observes that Kornhuber *et al.* (*J Neural Transm.* 106:857-867, 1999) disclose that the therapeutically relevant analgesic plasma concentrations of flupirtine are in the **low micromolar range** and that it acts like an NMDA receptor antagonist (*see* the Action, page 12). However, Kornhuber *et al.* do not refer to NMDA receptor antagonism when they say that flupirtine is active in the low micromolar range. Instead, they refer to flupirtine's effects on inwardly rectifying K+ channels, and even state that "under therapeutic conditions with serum concentrations of up to 5 μM, of the effects listed here, **only the effect on the inwardly rectifying K+ channel is relevant**" (*see* Table 1 and accompanying caption of Kornhuber *et al.*). Indeed, Kornhuber *et al.* empirically show that flupirtine's IC_{50} for antagonizing inward current responses to NMDA is closer to **200 μM** (*see* Figure 1B of Kornhuber *et al.*), well beyond the low micromolar range. Compared to the results for ketamine, using the same whole-cell configuration of the patch-clamp technique as

Kornhuber *et al.*, flupirtine's **so-called** "functional" NMDA antagonism is about **423 times weaker** than that of ketamine, the latter having an IC_{50} of **0.43 μM**. *See* Item 16 of the Adams Declaration; and Parsons *et al.*, *Eur. J. Neurosc.* 8:446-54, 1996. To consider ketamine and flupirtine as functional equivalents for antagonizing the NMDA receptor, and thus substitute flupirtine for ketamine according to the methods of Chizh *et al.*, a person of ordinary skill in the art would have had to consider using at least a 400-fold higher dose of flupirtine relative to ketamine, that is, a likely toxic and thus clinically-irrelevant dose. Applicants submit that a person of ordinary skill in the art would not have considered such a substitution to be clinically feasible.

Rather than NMDA antagonism, the empirical evidence at the time of filing all pointed towards the K_v7 channel as the primary mechanism by which flupirtine exerts its analgesic effects. This was first identified experimentally by Jakob and Krieglstein, followed by Kornhuber *et al.*, where flupirtine showed potent effects on inwardly rectifying K+ channels (at least 200x more potent than its effects on the NMDA receptor), and again by Wu *et al* (*J. Med. Chem. 46,* 3197-3200, 2003), where flupirtine was found to shift the activation curves toward negative voltages in KCNQ2/3 channels. *See also* Item 18 of the Adams Declaration, citing Passmore *et al.* (*J. Neurosci.* 23(18): 7227-7236, 2003) and Gribkoff (*Expert Opin. Ther. Targets.* 7(6): 737-48, 2003). Collectively, these reports and others unambiguously established that flupirtine was a KCNQ channel agonist because it targets the same family and subtypes of KCNQ channels, previously referred to as GIRK channels. Thus, at the date of filing, the mechanism of flupirtine had been empirically established as an opener of the newly characterized Kv7 channels, and not, as previously suspected (but never experimentally validated) as an antagonist of the NMDA receptor.

Overall, because the art prior to the time of filing had empirically established that flupirtine (unlike ketamine) was an opener of the newly characterized Kv7 channels, and only **indirectly** affected NMDA receptor currents at concentrations at least 423 times greater than ketamine, *i.e.*, at clinically-irrelevant concentrations, a person of ordinary skill in the art would have had no reasonable technical basis to substitute flupirtine for ketamine in a method for inducing an analgesic response in a mammal having neuropathic pain.

Based on the above and on previous remarks of record, Applicants submit that the **synergism** shown for the claimed combination of flupirtine and an opioid was entirely unexpected. Referring to the Examiner's observations at pages 14-15 of the Action, even assuming there were only three results to be expected (and Applicants disagree on this point) – **1**) an additive effect, **2**) a synergistic effect, **3**) and an antagonistic effect – it does not mean that a person of ordinary skill in the art could have predicted the actual result of synergism. It is one thing to expect an **effective** result for two agents allegedly known for the same purpose (*see* the Action, pages 9-10, carryover paragraph, and page 15), and another thing to expect a **synergistic** result. Synergism is somewhat rare in the pain therapy arts, relative to mere additive or even no cooperative effects, even for two agents known to have similar activity. Indeed, Chizh *et al.* did not report any synergism in their studies, and even stated that previous studies using ketamine in combination with the opioid alfentanil **failed to find any synergism**. *See* paragraph [0006] of Chizh *et al.*, citing Sethna *et al.*, *Anesth. Analg.* 86:1250-1256, 1998. Thus, without more evidence, a person of ordinary skill in the art would have had less than a reasonable chance of predicting synergism, and here, the only potential evidence for synergism appears to be the alleged functional equivalence between ketamine and flupirtine as NMDA receptor antagonists. Because such equivalence would not have been expected for ketamine and flupirtine, at least at clinically-relevant concentrations of flupirtine, there was insufficient technical evidence to predict synergism for the claimed flupirtine/opioid combination.

Also, there would have been no technical reason to expect synergism in the **absence of increased side-effects,** especially where flupirtine and opioids were individually known to share such side-effects. On this point, the Examiner appears to ignore numerous possible results in addition to the three noted above. Merely for illustration, such results include but are not limited to **1**) no beneficial effect on neuropathic pain but with increased side-effects, **2**) no beneficial effect on neuropathic pain with no increased side-effects, **3**) antagonistic effect on neuropathic pain with increased side-effects, **4**) antagonistic effect on neuropathic pain with no increased side-effects, **5**) additive effect on neuropathic pain with increased side-effects, **6**) additive effect on neuropathic pain with no increased side-effects, **7**) synergistic effect on neuropathic pain with increased side-effects, and **8**) synergistic effect on neuropathic pain with no increased side-effects, among others. For this example, that makes at least 8 possible results, and even assuming

straight odds for each result, a person of ordinary skill in the art would have only had a 12.5% chance of predicting the result shown by Applicants, that is, a synergistic effect on pain with no increased side-effects. Even straight odds could not have created a reasonable expectation of this result.

Applicants, however, submit that such odds are not straight, because it would have been more reasonable to expect an **increase** in shared side-effects. Indeed, there were many examples in the art of increased side-effects for opioid-based combination therapies. For instance, even though adjuvant/opioid therapy had been recommended for pain, Cleary taught that in his real-life experience of adjuvant therapy, "many patients...do not tolerate these medicines well and in fact **experience increased side effects**" (*see* page 127, column 2, last full sentence of Cleary, 2000) (emphasis added). Dionne achieved an additive increase in the analgesic effects of ibuprofen and opioids, but at the expense of **an increased incidence of adverse events** (*see* Dionne, *J Oral Maxillofac Surg.* 57:673-8, 1999). Likewise, de Craen *et al.* (*BMJ.* 313:321-325, 1996) found that the combination of paracetamol/codeine caused a significantly higher proportion of side effects compared to each agent alone. Hence, persons skilled in the art understood the difficulties in identifying effective, opioid-based combinations that do not have magnified, dose-related side effects, and would have set their expectations accordingly – that is, very low.

The Examiner also observes that the features upon which Applicants rely are not recited in the claims, for instance, the lack of increased sedation (a side effect common to both agents) and clinically-relevant concentrations. *See* the Action, page 16. The Examiner's point is well taken; however, Applicants respectfully submit that there is "no law requiring that unexpected results relied upon for patentability be recited in the claims." *Application of Merchant.* 575 F.2d 865, 869 (1978). Hence, the unexpected lack of overt sedation, for instance, need not be recited in the claims. Further, given the flupirtine-specific results of Kornhuber *et al.* relative to the ketamine-specific results of Parsons *et al.* (*i.e.,* flupirtine having a ~423-fold higher IC_{50} than ketamine for NMDA antagonism), Applicants respectfully submit that the concentrations of flupirtine required to achieve antagonism of the NMDA receptor would likely be toxic to humans, and thus by nature "clinically-irrelevant" to the claimed methods of treatment. To the extent necessary, Applicants submit that the claims already take into account the unexpectedly

synergistic results shown by Applicants, and kindly request the Examiner to re-consider this position.

To summarize, Applicants respectfully submit that a person of ordinary skill in the art at the time of filing would not have considered flupirtine an NMDA receptor antagonist at the time the instant application was filed. Likewise, such a person would not have considered flupirtine and ketamine as functional equivalents for antagonizing an NMDA receptor at clinically-relevant concentrations. Accordingly, it would not have been clinically feasible for a person of ordinary skill in the art to substitute flupirtine for ketamine on the basis that both are capable of antagonizing an NMDA receptor. For these and other reasons, Applicants submit that a person of ordinary skill in the art would have had no reasonable technical basis to expect **synergistic effects on neuropathic pain without increased side-effects** from a method of inducing an analgesic response in a mammal having neuropathic pain, comprising administering to the mammal a composition comprising flupirtine and an opioid, as claimed.

Because these unexpected synergistic results provide significant, practical advantages in the treatment of neuropathic pain, Applicants submit that secondary considerations of non-obviousness discussed herein and on the record are sufficient to overcome any alleged *prima facie* case of obviousness. It is also submitted that the same applies to dependent claim 46. Applicants therefore submit that the instant claims satisfy the requirements of non-obviousness, and respectfully request withdrawal of these rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants respectfully submit that no further impediments exist to the allowance of this application and, therefore, request an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

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Enclosures:

§ 1.132 Declaration of Professor David Adams, Ph.D
Information Disclosure Statement
1449
Non-Patent Litature Documents (28)